PET and SPECT Imaging of the Brain:

History, Technical Considerations, Applications, and Radiotracers

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ABSTRACT

Advances in nuclear medicine have revolutionized our ability to accurately diagnose patients with a wide array of neurologic pathologies and provide appropriate therapy. The development of new radiopharmaceuticals has made possible the identification of regional differences in brain tissue composition and metabolism. In addition, the evolution of three-dimensional molecular imaging followed by fusion with CT and MRI have allowed for more precise localization of pathologies. This review will introduce SPECT and PET imaging of the brain, including the history of their development, technical considerations, and a brief overview of pertinent radiopharmaceuticals and their applications.

Keywords: PET, SPECT, Radiology, Radiopharmaceutical, Tumor, Epilepsy, Dementia

HISTORY OF SPECT AND PET

Discoveries in the late 19th and early 20th centuries heralded the foundation of nuclear medicine as we know it today. The accidental identification of uranium radiation by Henri Becquerel in 1896 and Marie Curie's work and coinage of the term "radioactivity" in 1898 earned them the 1903 Nobel Prize in Physics.[1] Since then, numerous significant and seemingly insignificant discoveries have allowed for highly advanced developments in nuclear medicine and molecular imaging, more recently yielding powerful techniques such as amino acid positron emission tomographic (PET) imaging and peptide receptor radionuclide therapy. This review specifically covers molecular imaging of the brain with a focus on technical considerations and a brief introduction of the radiotracers and their applications.

SPECT and PET

The two mainstay modalities in nuclear medicine and molecular imaging of the brain include single photon emission computed tomography (SPECT) and PET. The inception time frames of SPECT and PET ran parallel in the 1950s and 1960s, utilizing computed tomography, which was described in radionuclide imaging prior to cross sectional anatomic X-ray tomographic imaging (1973).[2,3]

PET imaging was the first of the two modalities to be described, initially conceptualized in 1950 by Brownell and Sweet.[4] Not long thereafter, they published their work on three dimensional assessment of brain tumors with positron emission imaging.[5] In addition to evaluating brain tumors, much of the initial brain PET imaging

sought to characterize cerebral perfusion. At that time, multiple PET radiotracers were utilized to evaluate cerebral perfusion in animals, including iodine and thiopental derivatives, prior to the introduction of ^{14}C-deoxyglucose (^{14}C-DG) by Sokoloff.[6] After proof of concept of ^{14}C-DG in animal models, subsequent experiments were directed toward evaluation of human cerebral perfusion.

Meanwhile, Kuhl and Edwards were developing SPECT brain imaging, which they initially described in 1963[7] and optimized over multiple iterations, culminating in the Mark IV system in 1976.[8,9] They were able to evaluate focal brain pathology including intracranial masses (Figure 1) and hematomas (Figure 2) with the Mark IV system. Development of the Mark IV system was critically important for advancing PET cerebral perfusion imaging.

The ability to image living human brain function was realized with the introduction of ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Its positron emission, resulting in gamma photon creation, allowed for imaging of glucose utilization in living patients in the Mark IV system.[6] ^{18}F-FDG was first used on this system[10] and ultimately adapted for use in PET imaging in 1979.[11] ^{18}F-FDG is now the most widely used radiotracer in PET neuroimaging, thanks in large part to this landmark work.

Hybrid Imaging

While SPECT and PET imaging provide critical insight to functional aspects of neuropathology, they are not without limitations. The greatest of these limitations is arguably the lack of direct anatomic correlation. Uptake identifies functionality, but localizing the specific site of interest is difficult, leaving interpretation largely to expertise

of the interpreter. This limitation was circumvented with the introduction of hybrid functional and anatomic imaging with simultaneous SPECT/CT and PET/CT acquisition.

Hybrid SPECT/CT and PET/CT were introduced in 1994[12] and 1998[13], respectively. In the following few years, multiple studies demonstrated the clinical utility, benefits, and applications of hybrid imaging, specifically in oncologic imaging.[14-17] The introduction of hybrid imaging revolutionized the ability to localize functionality to a precise anatomic site. In the case of neuroimaging, brain pathology could be more easily identified to guide understanding of neurologic disease and direct therapies or neurosurgical interventions.

TECHNICAL CONSIDERATIONS

SPECT

After administration of a gamma photon emitting radiopharmaceutical, planar or SPECT imaging may be performed. SPECT imaging most commonly involves obtaining count data over 360 degrees of detector head rotation around the patient. This allows for data reconstruction in any planes necessary, including axial, sagittal, and coronal, and significantly improves localization and contrast resolution compared to planar imaging.

In the brain, this is especially useful. For example, gray and white matter can be differentiated from each other and deep structures, such as the basal ganglia, can be readily identified. Prior to SPECT, identifying potential seizure foci or differentiating radiation necrosis from tumor with planar imaging was not practical. With the advent of

SPECT with rotating detector heads, significant progress was made in brain imaging, and dedicated brain SPECT systems were also developed. These dedicated systems have promised greater spatial resolution and higher overall image quality[18], however come at a higher cost without the ability to image other organ systems. Most clinical practices must perform brain SPECT during a busy day imaging varying pathologies. This has led to the more widespread use of gamma cameras capable of imaging all organ systems, including the brain.

Radiopharmaceuticals useful in SPECT brain imaging (Table 1) are distributed throughout the body based on regional perfusion (^{99m}Tc-hexamethylpropyleneamine oxide [HMPAO] and ^{99m}Tc-ethyl cysteinate dimer [ECD]), active receptor transport (^{201}Tl and ^{123}I—FP-CIT [Ioflupane]), and passive diffusion and retention within specific cell types (^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin). Detailed discussion of these radiopharmaceuticals and their functions will be undertaken in subsequent sections.

Advantages of SPECT over PET imaging

While PET/CT is the better-known imaging modality, SPECT and hybrid imaging with SPECT/CT, do offer some advantages. For example, ^{99m}Tc-based radiopharmaceuticals impart a lower radiation dose compared to most positron emitters, which is especially important in pediatric patients, and SPECT imaging without CT also leads to lower radiation exposure compared to PET/CT. In addition, SPECT allows for dual isotope imaging. With most gamma cameras currently on the market, multiple photopeaks specific to the administered radiopharmaceuticals may be selected and simultaneously imaged, taking advantage of their different gamma photon emission

energies. These photopeaks can be separated during processing allowing for precise localization of uptake by each radiopharmaceutical, and work has already been done to demonstrate the success of this approach in Parkinson disease.[19] This method is not feasible with positron emitting radiopharmaceuticals, which all lead to the emission of 511 keV gamma photons.

Gamma cameras with SPECT and even SPECT/CT capabilities are less expensive than today's PET/CT and PET/MRI scanners. In addition, the ^{99m}Tc-based radiopharmaceuticals and ^{201}Tl employed in brain SPECT imaging are more readily available and less expensive compared to positron emitters, which are cyclotron produced.

Limitations of SPECT and SPECT/CT

SPECT and SPECT/CT imaging has several limitations compared to PET. More of the lower energy photons emitted by the radionuclides employed in brain SPECT (140 keV for ^{99m}Tc, 68-82 keV for ^{201}Tl, and 159 keV for ^{123}I) as compared to PET (511 keV) are absorbed and scattered within the patient, which means fewer photons are available to contribute to the image. In addition, metal collimation is required to remove scattered photons, which would otherwise significantly degrade the SPECT image. In fact, only a tiny fraction of photons leaving the patient make it to the detectors[20]; therefore, SPECT imaging is inherently lower count and higher in noise compared to PET, which has higher sensitivity due to coincidence detection. Because of this lower sensitivity, it also takes longer to collect the counts necessary to create a diagnostic SPECT image, which provides more opportunity for artifacts due to patient motion.

Spatial and contrast resolution are significantly lower with SPECT as compared to PET, which contribute to lower sensitivity in the detection of many disease processes.[21-24] Temporal resolution is inferior with SPECT imaging, as well, and absolute quantification of brain perfusion is not readily performed in the clinical setting. SPECT quantification is only now becoming more clinically available and is an active area of research,[25-27] while quantification of metabolism is performed in daily practice with ^{18}F-FDG PET.

Practically, the vast majority of PET scanners in operation in the US today are hybrid PET/CT cameras. With these scanners it is possible to optimize CT protocols in order to provide attenuation correction for PET data, localize pathologic processes, and characterize lesions with iodinated contrast. Most gamma cameras in the US, however, are not hybrid[28] and SPECT imaging without combined CT is quite common. This means exact anatomic localization and attenuation correction are not always possible, and more detailed information about brain lesions cannot be obtained. In addition, there are no SPECT/CT ICD-10 indications in brain imaging at this time.

All nuclear imaging is subject to artifact, and SPECT is no exception. In addition to those identified in planar imaging related to patient factors, collimators, and camera hardware, there are also artifacts specific to SPECT. For example, an error in the center of rotation or incorrectly aligned detector heads may cause false photopenic defects in tomographic images. Artifacts may also be introduced during reconstruction of the SPECT data. Regular and careful quality control must be undertaken to ensure all hardware and software are performing optimally.

All the advantages of hybrid SPECT/CT imaging also come with disadvantages. Patient motion may lead to misregistration and erroneous attenuation correction or even incorrect localization of radiopharmaceutical deposition.[29,30] These are similar to artifacts found in PET/CT and PET/MR imaging.[31]

While PET has many advantages over SPECT in brain imaging, advances in developing semiconductor gamma cameras with higher sensitivity, better spatial resolution, better energy resolution, and higher image quality,[32,33] as well as ongoing research in quantification hold the promise for significant improvements in SPECT and SPECT/CT brain imaging.[34]

PET

PET imaging relies upon the detection of photons emitted from a positron-emitting radiotracer to provide visual and quantitative information about the uptake of tracer within a patient. Similar to SPECT imaging, the radionuclide is tagged with a biologically active molecule, which distributes in the body according to a physiologic process. A PET tracer may, for instance measure metabolic activity (^{18}F-FDG), perfusion (^{13}N-NH3 or ^{82}Rb), somatostatin receptor density (^{68}Ga-DOTA-TATE), or amino acid metabolism (^{18}F-FET). A few of these tracers will be discussed in further detail in the applications section of this article. In contrast to single photon imaging, however, PET imaging offers several benefits from an imaging quality standpoint. In order to explain why this is the case, a brief explanation of the physics of PET is necessary.

Physical advantages of PET imaging

PET imaging relies on the principle of coincidence detection to produce an image. When a positron undergoes annihilation, it emits two 511 keV gamma photons at nearly opposite directions. These photons can be detected by PET detectors, which utilize this information to reconstruct an image. This principle of coincidence detection obviates the need for a physical collimator, providing PET imaging with an enormous image quality benefit relative to SPECT imaging. First, as described above, the absence of a collimator results in far more detected photons.[20,35] Secondly, although there is less of a theoretical limitation on the spatial resolution of SPECT relative to PET, the absence of a collimator in PET imaging removes the resolution/sensitivity tradeoff inherent in gamma imaging, meaning that in practice, the spatial resolution of PET imaging is significantly greater than that of SPECT.[36]

The vast majority of PET imaging devices in clinical use are hybrid units, coupled with a CT or MRI scanner. PET imaging alone does not provide the level of anatomic detail that CT or MRI provides, and fusion of the PET image with another modality allows precise anatomic localization of PET activity with a high-quality CT or MRI image. Another benefit of hybrid imaging with PET/CT or PET/MR is that it provides an efficient method of attenuation correction of the PET images. Hybrid PET/CT systems are much more widely available than hybrid SPECT/CT units.[28] Therefore, in many settings PET/CT may be the only hybrid modality available, which is another practical advantage of PET. Finally, emerging PET/MR systems are capable of providing hybrid imaging with a modality superior for most neuroimaging applications; however, SPECT/MR systems are not currently available for clinical use.

Limitations of PET imaging

Despite the inherent advantages provided by PET, there are tradeoffs, and the choice of modality often hinges not upon the inherent properties of the imaging modality, but rather upon the cost and availability of the radiotracer and imaging hardware. In other words, any potential advantages of one modality over another is rendered irrelevant if any component of the imaging procedure is unavailable or cost prohibitive.

PET radiopharmaceutical agents (Table 2) can be limited in availability for several reasons. First, a radiopharmaceutical requires regulatory approval before being utilized; thus, availability for clinical use will always be limited to the small pool of radiopharmaceuticals that have been approved. In the United States, approval for clinical use requires either a New Drug Application (NDA) or Investigational New Drug (IND) application to the Food and Drug Administration (FDA), both of which require a substantial investment of time and resources. Second, some PET radionuclides such as ^{11}C and ^{13}N have extremely short half-lives requiring an onsite cyclotron, thus limiting their widespread use.[20] Finally, even if practically attainable, some agents may not be reimbursed by commercial or government insurance payors. For example, Centers for Medicare and Medicaid Services (CMS) has decided to reimburse for the cost of amyloid PET of the brain only when the scan is obtained as part of an approved clinical trial.[37] This serves as an example of how high cost and a lack of reimbursement can serve to severely limit the clinical adoption of a radiopharmaceutical.

Finally, a discussion of PET imaging would not be complete without a discussion of artifacts. The vast majority of PET artifacts can be tied to the process of attenuation correction. Errors in attenuation correction can occur when PET and anatomic images are not precisely registered, usually due to patient motion between the PET and CT or MRI images (Figure 3). Other artifacts can occur when there is truncation of a portion of the anatomy on anatomic images, or when the attenuation values are not properly estimated due to artifacts present on the original image.[38] These artifacts are primarily problematic due to resultant inaccurate estimations of radiotracer uptake (standardize uptake values [SUVs]); however, misregistration artifact can also result in incorrect positioning of sites of uptake (Figure 4).[39] Patient motion during the PET image acquisition itself can also result in image degradation; however, these artifacts are encountered less frequently in PET than in SPECT imaging due to the shorter acquisition times made possible by PET.[40] Finally, there are artifacts that are unique to MR-based methods of attenuation correction; however, a detailed discussion of these is beyond the scope of this article. In summary PET is a powerful molecular imaging tool, but financial and regulatory challenges can serve to limit its use.

APPLICATIONS AND RADIOPHARMACEUTICALS

This discussion of applications and radiopharmaceuticals in PET and SPECT is meant to provide a superficial overview of the historic and current commonly used applications. For more detailed discussion of imaging of brain tumors, epilepsy, dementia, and brain tumor mimics, please see additional articles in this special issue.

Brain Tumors

CT is often the first imaging study in which an intracranial mass is identified, but MRI is the workhorse of brain tumor imaging. The superior tissue contrast resolution of MRI aided by gadolinium-based contrast agents makes it the ideal anatomic imaging modality for detailed evaluation of intracranial neoplasms and masses. Both CT and MRI are also valuable in assessing post-treatment response. Nuclear medicine imaging with SPECT and PET has historically played a complementary role in brain neoplasm imaging, often helping to narrow a differential diagnosis or to aid in treatment planning.

SPECT

Currently, SPECT is infrequently employed for the workup of brain tumors. This is largely due to the increased utilization of PET/CT and PET/MRI, which demonstrate better sensitivity, resolution, and potential for quantification compared to SPECT.[41] However, SPECT is much more widely available than PET scanning, and may still be useful in limited situations.

^{201}Tl

Thallium-201 is a potassium analog and was traditionally one of the more commonly used SPECT radiopharmaceuticals for evaluation of brain tumors. In its more recent application, ^{201}Tl SPECT can help differentiate post-radiation necrosis from tumor recurrence in evaluation of gliomas.[20] In general, the higher degree of activity noted in the suspicious region correlated with increased likelihood of tumor recurrence. The

differentiation between radiation necrosis and tumor recurrence in treated gliomas continues to be a diagnostic dilemma and a topic of extreme interest with newly developed PET radiopharmaceuticals.

PET

^{18}F-FDG

As previously mentioned, ^{18}F-FDG is a versatile and widely used PET radiotracer in oncologic imaging. ^{18}F-FDG is an analog of glucose, thus increased ^{18}F-FDG uptake is generally a marker for increased glucose metabolism. However, due to the high level of physiologic background uptake of ^{18}F-FDG in the brain, its use is limited in brain tumor evaluation. Nonetheless, there is a correlation between degree of ^{18}F-FDG uptake and glioma grade and survival.[42] In clinical settings, ^{18}F-FDG can also be used as an agent to attempt differentiation between radiation necrosis and tumor recurrence in treated high grade gliomas.

Amino acid PET

There has been considerable research and development of PET alternatives to ^{18}F-FDG for brain tumor imaging. Amino acid radiotracers have been well studied as alternatives and include L-(methyl-^{11}C)methionine (^{11}C-MET), O-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET), and 3,4-dihydroxy-6-(^{18}F)-fluoro-L-phenylalanine (^{18}F-FDOPA). These radiotracers have shown clinical value in evaluation of brain tumors in multiple clinical scenarios and are the recommended glioma PET imaging agents by the

Response Assessment in Neuro-Oncology (RANO) working group.[43] While ^{11}C- MET requires an onsite cyclotron due to its short half-life of 20 minutes, ^{18}F-FET and ^{18}F-FDOPA can be packaged and transported in a similar way to ^{18}F-FDG due to ^{18}F's longer half-life of 110 minutes. A recent meta-analysis showed that ^{11}C-MET and ^{18}F-FET PET had higher sensitivity for detecting glioma grade than ^{18}F-FDG PET.[44] A significant limitation to the use of amino acid radiotracers in the United States currently is lack of FDA approval for clinical use. The exception is ^{18}F-fluciclovine (Axumin®), which is a synthetic amino acid radiotracer currently FDA approved for imaging patients with biochemical relapse of prostate cancer. Recent studies have shown that ^{18}F-fluciclovine demonstrates high contrast between glioma uptake and background brain activity and shows its potential as a glioma imaging agent.[45-47]

SEIZURES AND EPILEPSY

The imaging evaluation of patients with a history of seizures commonly requires a multimodality approach, often combining conventional MRI and functional MRI with SPECT and PET. Unlike brain tumor evaluation, where SPECT has largely been replaced by PET, both SPECT and PET currently play vital roles in the workup of epilepsy.

SPECT

SPECT imaging in seizure evaluation is typically performed to lateralize or localize the epileptogenic cortex, and to help determine if a patient may be a surgical candidate.[48] SPECT imaging is performed with perfusion radiopharmaceuticals which

are lipophilic and readily cross the blood brain barrier. The two most used agents are ^{99m}Tc-HMPAO and ^{99m}Tc-ECD.

Imaging is typically performed at two different time points, either injecting radiopharmaceutical during a seizure (ictal) or between seizures (interictal), with subsequent SPECT imaging. Ictal imaging requires injection of radiopharmaceutical almost immediately following seizure onset, which is technically challenging and requires an organized program and experienced staff. When performed correctly, there should be increased perfusion to the epileptogenic site within the brain on SPECT imaging. Interictal SPECT is performed on patients who are not currently experiencing seizure activity, which is often confirmed by EEG. Typically, the degree of perfusion in interictal SPECT is lower than, or equal to background brain perfusion. Interictal SPECT can serve as a baseline to compare with ictal SPECT. MRI can also be co-registered to ictal and interictal SPECT to increase the sensitivity and specificity for detecting epileptogenic foci, a technique referred to as subtraction ictal SPECT co-registered to MRI (SISCOM).[49]

PET

^{18}F-FDG is the PET agent routinely used in evaluation of epilepsy. ^{18}F-FDG PET imaging is performed in an interictal state and, like SPECT, can be used for general localization and lateralization of seizure foci. Within an epileptogenic focus, ^{18}F-FDG uptake is usually decreased, showing a hypometabolic core that is typically larger than the epileptogenic focus. ^{18}F-FDG PET has a greater sensitivity in temporal lobe epilepsy than extratemporal lobe epilepsy.[48] Additional PET radiotracers have been studied for

use in seizure evaluation, including ^{11}C-flumazenil (FMZ) and an agent used in tuberous sclerosis patients, ^{11}C-methyl-l-tryptophan (AMT).[50] These radiotracers are not routinely used in clinical practice and further discussion is beyond the scope of this review.

DEMENTIA AND NEURODEGENERATIVE DISEASES

SPECT

SPECT radiopharmaceuticals used for the evaluation of dementia and neurodegenerative disorders are few. These include direct assessment via dopamine transporter (DaT) imaging with ^{123}I-Ioflupane, which is a substrate for striatal dopamine transporters, and ^{99m}Tc-HMPAO, a cerebral perfusion agent which allows for indirect assessment of cerebral metabolism.

DaT

DaT SPECT provides an avenue for differentiating patients with dementia with Lewy bodies (DLB), Parkinson disease (PD), and Parkinson-plus syndromes from other dementia subsets.[51-53] Mechanistically, DLB and PD are characterized by impaired dopamine homeostasis, manifested by decreased dopaminergic neurons and decreased radiopharmaceutical uptake in dopaminergic pathways on DaT SPECT. This characteristic loss of dopaminergic neurons has shown to help differentiate DLB from other dementias, such as Alzheimer disease.[54,55] In the setting of PD, selective radiopharmaceuticals and protocols have allowed for further differentiation of patients with the akinetic-rigid PD phenotype as compared to patients with the tremor dominant

PD phenotype.[56] Overall, DaT SPECT has shown great promise as an in vivo method to accurately diagnose DLB, PD, and Parkinson-plus syndromes.[57] Further discussion of DaT SPECT in these entities will be undertaken in subsequent articles.

^{99m}Tc-HMPAO

Evaluation of dementia through imaging of altered cerebral perfusion has been demonstrated with ^{99m}Tc-HMPAO. Patterns of radiopharmaceutical uptake have been shown to correlate with anatomic abnormalities seen on cross-sectional imaging. In fact, molecular neuroimaging with ^{99m}Tc-HMPAO has been suggested to be a more sensitive test than anatomic imaging when evaluating patients with dementia.[58]

Though SPECT imaging may help differentiate between dementia subsets, there has been speculation that ^{18}F-FDG PET may be superior to SPECT.[22] Evidence for this statement has been called into question, however, with the need for further comparison of the accuracy of ^{18}F-FDG PET and cerebral perfusion SPECT.[59]

PET

Much of the molecular imaging evaluation of dementia and neurodegenerative diseases is conducted with PET imaging. Multiple radiotracers are currently available and there is active investigation into additional agents, specifically in the evaluation of Alzheimer dementia.

^{18}F-FDG PET

^{18}F-FDG is the most widely used radiotracer for PET imaging of dementia in the United States and the utility of ^{18}F-FDG PET in dementia was reviewed as early as 1989.[60] Glucose metabolism is directly related to neuronal functional activity, therefore neurodegeneration is associated with decreased uptake.[61] Advances through the years have led to broadened applications for ^{18}F-FDG PET, including its use as a biomarker for dementia and in evaluating progression from mild cognitive impairment to dementia.[62]

Amyloid β PET

Novel amyloid beta (Aβ) radiotracer agents that label the Aβ plaques of Alzheimer disease patients have been available in some capacity since 2012. Currently, there are three FDA approved ^{18}F-labeled Aβ radiotracer agents, including florbetapir (Amyvid®), florbetaben (Neuraceq®) and flutemetamol (Vizamyl®).[63-65] A recent systematic review demonstrated the clinical utility of Aβ PET imaging with significant management changes and revision of clinical diagnoses in nearly one third of patients.[66]

Tau PET

Additional PET imaging of Alzheimer's disease is directed toward labeling of misfolded tau proteins. These radiotracers, such as flortaucepir, may be of clinical utility in the future, but their use is currently limited to research (clinicaltrials.gov, NCT03040713 and NCT03901105).

CONCLUSION

We have provided a review of the history, technical considerations, and common radiopharmaceuticals employed for PET and SPECT imaging of the brain. Additionally, we have introduced multiple important nuclear medicine applications for brain imaging, which will be addressed in greater detail in subsequent articles in this special edition. Such applications of nuclear imaging for brain pathology are numerous and research of novel nuclear imaging agents and techniques is robust. Ongoing investigations in nuclear medicine and molecular imaging hold the promise to further expand our ability to characterize the cellular function and composition of the brain, advance neurologic disease diagnostics, and potentially improve patient care outcomes.

REFERENCES

1. Tretkoff E. This month in physics history: March 1, 1896: Henri Becquerel discovers radioactivity. *American Physical Society News*2008.
2. Ambrose J, Hounsfield G. Computerized transverse axial tomography. *Br J Radiol.* 1973;46(542):148-149.
3. Hounsfield GN. Computerized transverse axial scanning (tomography). 1. Description of system. *Br J Radiol.* 1973;46(552):1016-1022.
4. Brownell GL. *A history of positron imaging.* Massachusetts General Hospital;1999.
5. Brownell GL, Sweet WH. Localization of brain tumors with positron emitters. *Nucleonics.* 1953;11:40-45.
6. Sokoloff L. Louis Sokoloff. In: Squire LR, ed. *The history of neuroscience in autobiography.* Vol 1. Washington DC: Society for Neuroscience; 1996:454-497.
7. Kuhl DE, Edwards RQ. Image separation radioisotope scanning. *Radiology.* 1963;80(4):653-661.
8. Kuhl DE, Edwards RQ. The Mark III scanner: A compact device for multiple-view and section scanning of the brain. *Radiology.* 1970;96(3):563-570.
9. Kuhl DE, Edwards RQ, Ricci AR, Yacob RJ, Mich TJ, Alavi A. The Mark IV system for radionuclide computed tomography of the brain. *Radiology.* 1976;121(2):405-413.
10. Reivich M, Kuhl D, Wolf A, et al. The [18F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res.* 1979;44(1):127-137.

11. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: Validation of method. *Ann Neurol.* 1979;6(5):371-388.
12. Blankespoor SC, Hasegawa BH, Brown JK, et al. Development of an emission-transmission CT system combining X-ray CT and SPECT. Paper presented at: Proceedings of 1994 IEEE Nuclear Science Symposium - NSS'94; 30 Oct.-5 Nov. 1994, 1994.
13. Townsend DW, Beyer T, Kinahan PE, et al. The SMART scanner: A combined PET/CT tomograph for clinical oncology. Paper presented at: 1998 IEEE Nuclear Science Symposium Conference Record. 1998 IEEE Nuclear Science Symposium and Medical Imaging Conference; 8-14 Nov. 1998, 1998.
14. Beyer T, Townsend DW, Brun T, et al. A combined PET/CT scanner for clinical oncology. *J Nucl Med.* 2000;41(8):1369-1379.
15. Bocher M, Balan A, Krausz Y, et al. Gamma camera-mounted anatomical X-ray tomography: technology, system characteristics and first images. *Eur J Nucl Med.* 2000;27(6):619-627.
16. Patton JA, Delbeke D, Sandler MP. Image fusion using an integrated, dual-head coincidence camera with X-ray tube-based attenuation maps. *J Nucl Med.* 2000;41(8):1364-1368.
17. Tang HR, Da Silva AJ, Matthay KK, et al. Neuroblastoma imaging using a combined CT scanner-scintillation camera and 131I-MIBG. *J Nucl Med.* 2001;42(2):237-247.

18. Stam MK, Verwer EE, Booij J, Adriaanse SM, de Bruin CM, de Wit TC. Performance evaluation of a novel brain-dedicated SPECT system. *EJNMMI Phys.* 2018;5(1):4.

19. Ichise M, Ballinger JR. SPECT imaging of dopamine receptors. *J Nucl Med.* 1996;37(10):1591-1595.

20. Mettler FA, Guiberteau MJ. *Essentials of Nuclear Medicine and Molecular Imaging.* 7th ed. Philadelphia, PA: Elsevier; 2019.

21. Kim S, Mountz JM. SPECT imaging of epilepsy: An overview and comparison with F-18 FDG PET. *Int J Mol Imaging.* 2011;2011:813028.

22. O'Brien JT, Firbank MJ, Davison C, et al. 18F-FDG PET and perfusion SPECT in the diagnosis of Alzheimer and Lewy body dementias. *J Nucl Med.* 2014;55(12):1959-1965.

23. Parker MW, Iskandar A, Limone B, et al. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: a bivariate meta-analysis. *Circ Cardiovasc Imaging.* 2012;5(6):700-707.

24. Spencer SS. The relative contributions of MRI, SPECT, and PET imaging in epilepsy. *Epilepsia.* 1994;35 Suppl 6:S72-89.

25. Armstrong AJ, Anand A, Edenbrandt L, et al. Phase 3 assessment of the automated bone scan index as a prognostic imaging biomarker of overall survival in men with metastatic castration-resistant prostate cancer: A secondary analysis of a randomized Clinical Trial. *JAMA Oncol.* 2018;4(7):944-951.

26. Dickson J, Ross J, Voo S. Quantitative SPECT: The time is now. *EJNMMI Phys.* 2019;6(1):4.

27. Suh MS, Lee WW, Kim YK, Yun PY, Kim SE. Maximum standardized uptake value of (99m)Tc hydroxymethylene diphosphonate SPECT/CT for the evaluation of temporomandibular joint disorder. *Radiology.* 2016;280(3):890-896.

28. Knollmann D, Avondo J, Schaefer WM. Is hybrid SPECT/CT necessary for pre-interventional 3D quantification of relative lobar lung function? *Eur J Hybrid Imaging.* 2018;2(1):18.

29. Goetze S, Brown TL, Lavely WC, Zhang Z, Bengel FM. Attenuation correction in myocardial perfusion SPECT/CT: effects of misregistration and value of reregistration. *J Nucl Med.* 2007;48(7):1090-1095.

30. Takahashi Y, Murase K, Higashino H, Mochizuki T, Motomura N. Attenuation correction of myocardial SPECT images with X-ray CT: Effects of registration errors between X-ray CT and SPECT. *Ann Nucl Med.* 2002;16(6):431-435.

31. Lee TC, Alessio AM, Miyaoka RM, Kinahan PE. Morphology supporting function: attenuation correction for SPECT/CT, PET/CT, and PET/MR imaging. *Q J Nucl Med Mol Imaging.* 2016;60(1):25-39.

32. Abbaspour S, Mahmoudian B, Islamian JP. Cadmium telluride semiconductor detector for improved spatial and energy resolution radioisotopic imaging. *World J Nucl Med.* 2017;16(2):101-107.

33. Takahashi Y, Miyagawa M, Nishiyama Y, Ishimura H, Mochizuki T. Performance of a semiconductor SPECT system: Comparison with a conventional Anger-type SPECT instrument. *Ann Nucl Med.* 2013;27(1):11-16.

34. Toyonaga T, Shiga T, Suzuki A, et al. New SPECT scanner with semiconductor detectors enables quantitative dual tracer diagnostic imaging of CBF and Dopamine transporter imaging in patients with cognitive disorder. *J Nucl Med.* 2016;57(Supplement 2):108.

35. Bushberg JT, Seibert JA, Leidholdt EM. *Essential Physics of Medical Imaging.* Philadelphia, PA: Wolters Kluwer Health; 2011.

36. Rahmim A, Zaidi H. PET versus SPECT: Strengths, limiations and challenges. *Nucl Med Commun.* 2008;29(3):193-207.

37. Maschke KJ, Gusmano MK. Medicare and amyloid PET imaging: The battle over evidence. *J Aging Soc Policy.* 2017;29(2):105-122.

38. Sureshbabu W, Mawlawi O. PET/CT imaging artifacts. *J Nucl Med Technol.* 2005;33(3):156-161; quiz 163-154.

39. Mawlawi O, Pan T, Macapinlac HA. PET/CT imaging techniques, considerations, and artifacts. *J Thorac Imaging.* 2006;21(2):99-110.

40. Garcia EV. Physical attributes, limitations, and future potential for PET and SPECT. *J Nucl Cardiol.* 2012;19 Suppl 1:S19-29.

41. Bag A, Almodovar S. Molecular imaging: PET and SPECT. In: Jain R, Essig M, eds. *Brain Tumor Imaging.* New York: Thieme; 2015:156-169.

42. Padma MV, Said S, Jacobs M, et al. Prediction of pathology and survival by FDG PET in gliomas. *J Neurooncol.* 2003;64(3):227-237.

43. Albert NL, Weller M, Suchorska B, et al. Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations

for the clinical use of PET imaging in gliomas. *Neuro Oncol.* 2016;18(9):1199-1208.

44. Katsanos AH, Alexiou GA, Fotopoulos AD, Jabbour P, Kyritsis AP, Sioka C. Performance of 18F-FDG, 11C-Methionine, and 18F-FET PET for glioma grading: A meta-analysis. *Clin Nucl Med.* 2019;44(11):864-869.
45. Bogsrud TV, Londalen A, Brandal P, et al. 18F-Fluciclovine PET/CT in suspected sesidual or recurrent high-grade glioma. *Clin Nucl Med.* 2019;44(8):605-611.
46. Michaud L, Beattie BJ, Akhurst T, et al. (18)F-Fluciclovine ((18)F-FACBC) PET imaging of recurrent brain tumors. *Eur J Nucl Med Mol Imaging.* 2019.
47. Parent EE, Benayoun M, Ibeanu I, et al. [(18)F]Fluciclovine PET discrimination between high- and low-grade gliomas. *EJNMMI Res.* 2018;8(1):67.
48. Ergun EL, Saygi S, Yalnizoglu D, Oguz KK, Erbas B. SPECT-PET in epilepsy and clinical approach in evaluation. *Semin Nucl Med.* 2016;46(4):294-307.
49. Sidhu MK, Duncan JS, Sander JW. Neuroimaging in epilepsy. *Curr Opin Neurol.* 2018;31(4):371-378.
50. Juhasz C, John F. Utility of MRI, PET, and ictal SPECT in presurgical evaluation of non-lesional pediatric epilepsy. *Seizure.* 2019.
51. Garriga M, Mila M, Mir M, et al. (123)I-FP-CIT SPECT imaging in early diagnosis of dementia in patients with and without a vascular component. *Front Syst Neurosci.* 2015;9:99.
52. Siepel FJ, Rongve A, Buter TC, et al. (123I)FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study. *BMJ Open.* 2013;3(4).

53. van der Zande JJ, Booij J, Scheltens P, Raijmakers PG, Lemstra AW. [(123)]FP-CIT SPECT scans initially rated as normal became abnormal over time in patients with probable dementia with Lewy bodies. *Eur J Nucl Med Mol Imaging.* 2016;43(6):1060-1066.

54. McKeith I, O'Brien J, Walker Z, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurol.* 2007;6(4):305-313.

55. Walker Z, Jaros E, Walker RW, et al. Dementia with Lewy bodies: A comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *J Neurol Neurosurg Psychiatry.* 2007;78(11):1176-1181.

56. Eggers C, Kahraman D, Fink GR, Schmidt M, Timmermann L. Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of FP-CIT single photon emission computed tomography. *Mov Disord.* 2011;26(3):416-423.

57. Suwijn SR, van Boheemen CJ, de Haan RJ, Tissingh G, Booij J, de Bie RM. The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism: a systematic review. *EJNMMI Res.* 2015;5:12.

58. Swan A, Waddell B, Holloway G, et al. The diagnostic utility of 99mTc-HMPAO SPECT imaging: a retrospective case series from a tertiary referral early-onset cognitive disorders clinic. *Dement Geriatr Cogn Disord.* 2015;39(3-4):186-193.

59. Davison CM, O'Brien JT. A comparison of FDG-PET and blood flow SPECT in the diagnosis of neurodegenerative dementias: a systematic review. *Int J Geriatr Psychiatry.* 2014;29(6):551-561.

60. Hoffman JM, Guze BH, Baxter LR, Mazziotta JC, Phelps ME. [18F]-fluorodeoxyglucose (FDG) and positron emission tomography (PET) in aging and dementia. A decade of studies. *Eur Neurol.* 1989;29 Suppl 3:16-24.

61. Sokoloff L. Localization of functional activity in the central nervous system by measurement of glucose utilization with radioactive deoxyglucose. *J Cereb Blood Flow Metab.* 1981;1(1):7-36.

62. Tripathi M, Tripathi M, Parida GK, et al. Biomarker-based prediction of progression to dementia: F-18 FDG-PET in amnestic MCI. *Neurol India.* 2019;67(5):1310-1317.

63. FDA. US prescribing information for Amyvid. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202008s000lbl.pdf. Published 2013. Accessed2020.

64. FDA. US prescribing information for Neuraceq. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf. Published 2014. Accessed2020.

65. FDA. US prescribing information for Vizamyl. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203137s005lbl.pdf. Published 2016. Accessed2020.

66. Fantoni ER, Chalkidou A, JT OB, Farrar G, Hammers A. A systematic review and aggregated analysis on the impact of amyloid PET brain imaging on the diagnosis, diagnostic confidence, and management of patients being evaluated for Alzheimer's disease. *J Alzheimers Dis.* 2018;63(2):783-796.

FIGURES

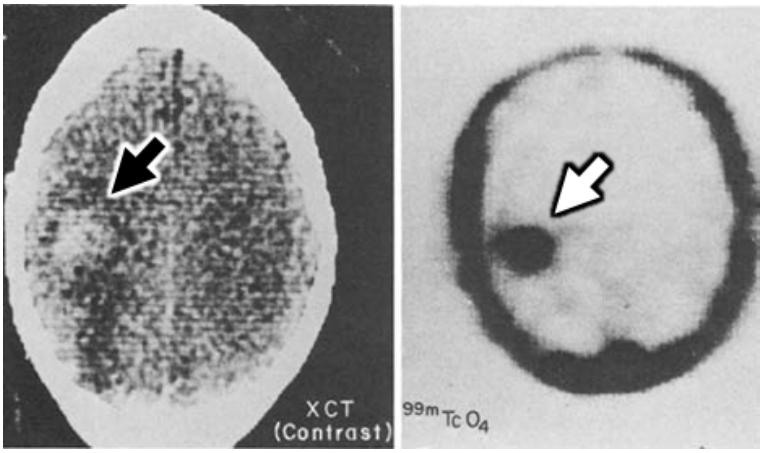

Figure 1. Brain metastasis. 52-year-old male with intracranial metastatic bronchogenic carcinoma. Due to altered blood brain barrier mechanics, a right cerebral hemisphere metastasis is identified on the post-contrast CT imaging (closed arrow) with corresponding radiopharmaceutical uptake on SPECT (open arrow). Published with permission granted by RSNA®, originally published as Figure 8 in: Kuhl, DH, Edwards, RQ, Ricci, AR, et al. The mark IV system for radionuclide computed tomography of the brain. *Radiology*. 1976;121:405-413.

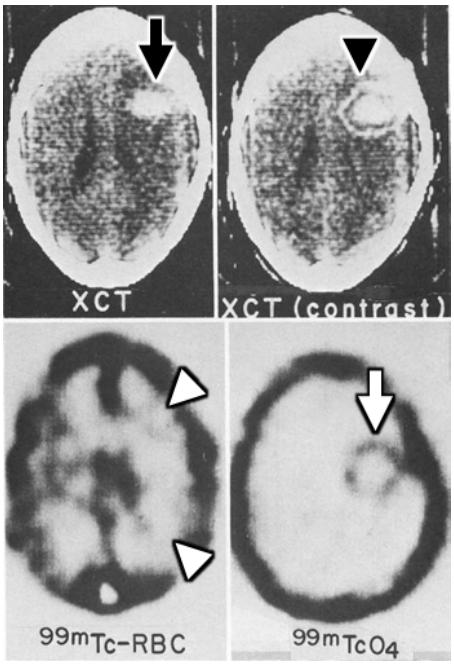

Figure 2. Intracerebral hematoma. 17-year-old with intraparenchymal hematoma (hematoma present for 2 weeks). Pre-contrast CT (XCT) demonstrates high attenuation hematoma (closed arrow) with surrounding “halo” of enhancement on postcontrast CT (XCT [contrast]) (closed arrowhead) secondary to hyperemia or altered blood brain barrier. Radiolabeled red blood cells (^{99m}Tc-RBC) demonstrate decreased ipsilateral cerebral blood volume (open arrowheads) and altered blood brain barrier surrounding the hematoma ($^{99m}TcO_4$) (open arrow). Published with permission granted by RSNA®, originally published as Figure 9 in: Kuhl, DH, Edwards, RQ, Ricci, AR, et al. The mark IV system for radionuclide computed tomography of the brain. *Radiology*. 1976;121:405-413.

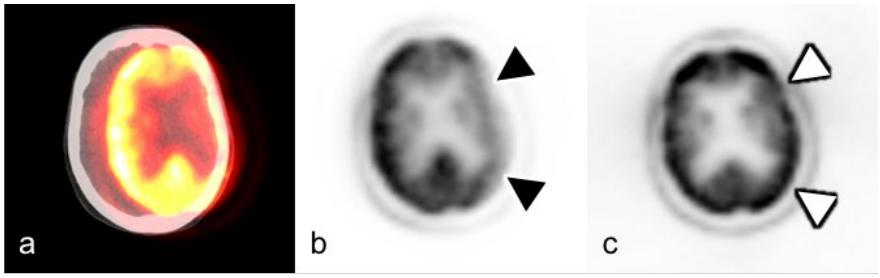

Figure 3. Misregistration due to motion. Misregistration due to patient motion between CT and PET acquisition after injection of ^{18}F-FDG (a) results in a large area of apparent reduced uptake along the periphery of the left cerebral hemisphere (closed arrowheads) on the attenuation corrected (AC) PET images (b). Symmetric uptake in this area on the non-AC images (open arrowheads) confirms the artifactual nature of this finding (c).

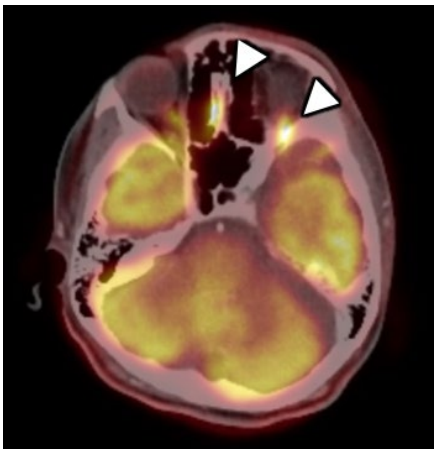

Figure 4. Misregistered sites of uptake. Fused ^{18}F-FDG PET/CT image shows misregistered activity originating from the extraocular muscles simulating pathologic sites of activity at the cribriform plate and at the greater wing of the left sphenoid bone (open arrows). The underlying bone was normal on the unfused CT (not shown). Diffuse extraocular muscle uptake can be a normal finding, resulting from physiologic glucose utilization secondary to ocular motion during the equilibration period.

TABLES

Table 1. SPECT Radiopharmaceuticals

Radiopharmaceutical	Photons (keV)	Production	Dose (mCi)*	Physical half life
Thallium-201	68-82	Cyclotron	3-5	73 hours
Technetium-99m HMPAO ECD	140	Generator	15-30	6 hours
I-123 Ioflupane	159	Cyclotron	3-5	13 hours

*Adult doses for brain specific indications, such as tumor recurrence, cerebral perfusion, and dopamine transporter imaging.

Table 2. PET Radiopharmaceuticals

Radiopharmaceutical	Production	Dose (mCi)	Physical half life
Fluorine-18	Cyclotron		110 minutes
FDG		5-20	
FDOPA		5	
Fluciclovine		5-10	
Florbetapir		10	
Florbetaben		8.1	
Flutemetamol		5	
Flortaucepir		10	
Carbon-11 methionine	Cyclotron	5-7	20 minutes

*Photons generated in PET imaging are paired 511 keV photons as described in "Technical Considerations."